Johnstone (A. W.)

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THE FUNCTION AND PATHOLOGY OF THE RETICULAR TISSUE.*

BY A. W. JOHNSTONE, M. D., CINCINNATI, OHIO.

The function of the reticular tissue is to furnish protoplasm, which supplies the waste of the daily wear and tear of the body. This is the conclusion I have reached after twenty years of study.

This train of thought was first started in your midst. In the winter of 1876, a pupil on the benches of the new University building, I was one day listening to Prof. Darby lecture on skin grafting. The next lecture was by Prof. Arnold, on the function of the white blood cells. At that time we had just found that they wandered, as Cohnheim's ideas were just beginning to be adopted by our schools. The phagocytic action was little understood, and, though the lecture was clear as far as it went, it did not give us the ultimate purposes for which this wandering takes place. In thinking over the possible purposes for which these migrations were made, the idea came to me, Is it possible that they may take the place of the fixed tissue cells, and that in this way the repair of the body is made? During the same course of lectures, Prof. Arnold gave us a great many illustrations of the immense amount of waste that is constantly taking place in what were once protoplasmic bodies, the wholesale destruction of epithelium in the secretion of milk, the rapid deterioration of epithelial cells caused by the secretion of mucus and sebaceous fluids, and, in fact, the rapid wearing away of epithelial structures wherever any functional activity takes place. But nowhere could he give us what seemed to me an adequate answer to, "Whence comes the supply to repair this waste?" This, gentlemen, has been the central idea of all my studies.

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* Read, by invitation, before the New York Obstetrical Society, May 5, 1896.

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The first experiment I made on the subject was going over again the old experiments of Onimus, who claimed to prove that the leucocytes originated *de novo* from a blastema, by putting the serum of freshly drawn blisters in gold-beater skin bags in the cellular tissue of animals, and finding after twenty-four hours large numbers of leucocytes swimming in the serum. These, I believed, got there by migration, and proved it by varying his experiments. First, I found that the thickness of the bag measured the time in which the leucocytes would be found. Where there was only one layer of gold-beater skin, the leucocytes would appear in twenty-four hours, as he had said. Where there were two layers, it took forty-eight hours; where there were three layers, still longer. But when I used a varnished gold-beater skin, through which no migration could take place, no matter how long the bag was left in position, the leucocytes did not appear. I also found it made no difference what kind of fluid, so that it was not irritating, was placed inside this bag—that the leucocytes would come just the same. A mixture of water and the white of egg, pure water, simple saline solutions, etc., were all tried with the same result. So I was convinced that he had overlooked the migratory power of the white blood cells, and consequently his reasoning had to fall to the ground.

I next turned to the study of the reticular tissue, to find if possible how these cells originated, and in it I discovered the gemmation of the granule from the thread, which formed the future nucleus of the cell. It is true there is a certain amount of cellular division after the cell had grown, but it does not amount to a great deal in the supply of the tremendous waste which is necessarily taking place among the leucocytes all the time. Immense numbers of them are used up in every conceivable way, and the latest investigations of the digestion of fats shows that very large numbers of leucocytes —far beyond what we have been taught heretofore—necessarily must be killed in the process of the absorption of fat. The one thing that made me a rebel to karyokinesis as the sole method of production was the fact I learned as a boy, while studying vegetable life, that the vitality in the bulbous variety of plants is always one of diminishing quantity. Take for illustration the common potato, the simplest form of cell division. All of you who are country boys know how this grows, but you also know, unless you go back to the seed and get a new variety, that in ten or twelve years the potato will have completely run out. This law holds good for all tubers.

Cell division, as we understand it, does very well for a short time, but if that is the only source from which the vital forces are drawn, sooner or later it must run out and the line become extinct. I have always believed it to be an exceptional power, which Nature uses only upon exceptional occasions, when something must be done rapidly, but for a short time, and to me cell division, as we understand it, always means a weakened tissue. With this belief deeply ingrained into my thoughts, it is no wonder I have pushed on, hunting for some direct connection with the nervous system for the life-giving power of our protoplasm.

The first publication of the fact of the budding of the granule was made in 1878, and you will find it in Dr. Heitzman's *Microscopical Morphology*, in whose laboratory I made the discovery, and to whose kindness and support I owe much for the pleasure I have had in my microscopical studies. From 1878 to 1886 I was still so imbued with the idea of cell division that I hunted for it in all its forms in all healthy adult tissues, but could never find it in a degree anything like proportionate to the amount of waste of the structure itself. During this time I turned to the waste of epithelium, and tried to find its supply. It is true in the rete Malpighii of the skin you do find cell division going on, but nothing like in the proportion of the desquamation which we have from the corneous layer. How much this desquamation is we surgeons now have practical knowledge of. Whenever you have been traveling, cut off from your bath tub for a few days, your first soap bath gives you an idea of the millions of these cells that have been got rid of. Did any of you ever take the trouble to put the settlings of the bath tub under the microscope? If by any accident you have failed to take your bath regularly every day, the amount of cell destruction found is something simply terrible.

Knowing all this, I studied not only the skin but the nails, the frog of the horse's foot, and many other epithelial structures of cornigerous nature, but I found them so extremely hard to handle and so difficult to deal with that nothing very satisfactory could be made out; though in the frog of a colt's foot, about 1880, I did see this same budding. One winter I spent in the Bahama Islands, and in the fish's scale and the turtle's shell that I there looked into I found something approximating the same thing, but my idea of cell division was so thoroughly grounded I still did not understand what this budding of the granule meant.

The methods I used in handling these structures were the same old ones we were all taught in the laboratories, and that I am sorry to say are still in vogue with a great many men—that is, of first hardening the tissues, putting them through very tedious processes, which converts them almost into leather before you attempt to cut them. In 1886, though, I found a very convenient little freezing microtome in Edinburgh, and my experience with that taught me all this hardening is not necessary, and that it rather hampers the clearness of definition than to give any advantage to it. In the preparation of my specimens, from which the menstrual organ paper was worked out for the British Gynæcological Society in 1886, I found the sooner the specimen was got on the freezing stage after it was removed from the body of the animal the better the results would be. All that was necessary after slicing it as thin as possible was to let it lie in water for a few hours until the air bubbles caused by the freezing were soaked out, then either to mount it in glycerin and seal it up with asphalt, or, if you want a beautiful specimen, it might be stained with carmine. But, to the practiced eye, this staining is not necessary. This is the method I have uniformly used, and the one that gives most satisfactory results. The objection of many to it is that your specimens will not keep, which is a mistake. I have in my possession now specimens that were made in this way ten years ago, and, where the asphalt has not cracked and allowed the glycerin to evaporate, they are just as clear and perfect as they were the day they were cut.

While we are on the subject of preparation of specimens, I want to enter a protest against the tedious processes that I see many of my *confreres* using, and above all, the habit of mounting in Canada balsam. The high refracting power of Canada balsam blurs the specimen, and in very high powers, from fifteen hundred up, its clearness of definition is nothing like equal to the glycerin specimen.

But the one thing that has been the greatest assistance to me is this little freezing microtome. It is very simple, no trouble about being kept clean, and, with the specimen frozen, it cuts the hard quill of a feather and the soft gelatinous pulp in a beautiful even plane that I have seen the rocking microtome simply make hash of. The rolling of the specimen, which so many complain of, with a little care is got rid of in the water that soaks out the air bubbles. So that with this little machine I can make specimens three or four

times larger than any cover glass will accommodate, with every imaginable density of structure lying within it.

I will not take up your time in a repetition of the conclusions given in the menstrual organ paper of 1886. They were so beautifully presented to this body by Dr. Pryor last fall that it would be a waste of time for me to here discuss them. At the time that paper was written I thought it simply a digression from the subject I had been so long pursuing, and the only light it gave me was that the single layer of columnar epithelium lining the cavity of the uterus was produced directly from the subjacent protoplasm, but that was the only step given me in the right direction. My previous studies of lymphoid structures were so thorough that I could not be deceived as to the nature of the human endometrium. But even then I thought it somewhat of an exception, and did not dream that it is the type of all tissue regeneration.

The lymphoid nature of the endometrium thoroughly established gave me the key to the whole situation, and all that was necessary to find the zoölogical nature of the endometrium was to follow up this clew. The results you know. While it is true I did feel I had done a good piece of work in properly classifying the endometrium, as I have stated, I thought it a mere digression from my main quest. But this deviation had to be pursued further. The winter of 1886 and 1887 I devoted to the comparative study of the endometrium in the cycle of the rut. This paper I sent to the British Gynæcological Society, and you will find it on page 379 of the *British Gynæcological Journal* for 1887. The reasoning there going to show the necessity for the lymphoid nature of the endometrium is entirely too long here to consider. All that is necessary is to repeat that the lymphoid state, as in the human being, is an absolute necessity to an individual in whom the rut is omnipresent. But there is no way by which the human placenta could be manufactured in such a short time unless we had the protoplasm just ready to go into the myeloid state. From this I also learned that the myeloid state is reached by other routes, which are only an approximation to the transitions described for the human endometrium, and that in the dog and many other lower animals there is a condition very closely resembling that found in the monkey by Mr. Heape. In them the myeloid state is also reached, but at much longer intervals, and when nature is thoroughly prepared for it. I can not stop now to discuss the varying condition of these endometria, for nothing short of a course of lec-

tures could possibly present these varying conditions in an intelligible shape. The only reason that I have mentioned this paper is to show you that its preparation was the turning point in my ideas as to the real production of epithelium. Not that I saw any very great changes in the epithelium of the uterus as the rut approaches, but I found enough to convince me that the protoplasm of the epithelium acted very much like the protoplasm of the connective tissue; and that, after all, protoplasm, no matter whether it is an epithelial cell or a connective-tissue cell, myeloid state, or what not, is protoplasm at last, and is acted upon in very much the same way by any very great nerve stimulation. After studying the rut, I naturally turned to thinking about the molt in birds, wondering if it was an analogous process. It seemed to me to be rather the trough of the wave, if the rut represented the crest, and thought I might find something in studying the changing histological conditions of the formation of feathers. So, along through 1888 and 1889, I put in my spare time in studying the varying conditions of the feather papilla, and there found that the feather papilla is a very closely analogous substance to the endometrium; and that, like the endometrium in the lower animals—that is, when the feather is full grown—it is nothing but myxomatous tissue. But when the molt comes on and the new feather about to be grown; the whole mucous tissue is rapidly converted into a very large protoplasmic mass, which an expert can scarcely differentiate from ordinary adenoid structures.

In the spring of 1889 I was asked to read a paper before the obstetrical branch of the British Medical Association, and I took as my theme the sexual ornaments, and there showed some beautiful drawings, made by my first teacher, Dr. Heitzman, with the greatest of care, portraying fully these rapid and beautiful changes which take place in the quiet, silent myxomatous tissue as it rapidly springs into the new protoplasmic life, builds up the columns of the feather, and in a very short time constructs such a large epithelial formation. From the study of the feather papilla, I was sure that the two were alike, and took the ground that the manufacture of the sexual ornaments was only an analogous process to the manufacture of the protoplasm necessary to make the afterbirth. This paper was read at the Leeds meeting of the British Medical Association, in the summer of 1889. For some reason, I never knew what, it was not published, and to my great sorrow the drawings were lost. It is true at that time my views about the reproduction

of epithelium were somewhat crude, though it was a step in the right direction, and put me on the track of the discoveries that I here bring you to-night. After my return from England in 1889, my business was so engrossing that all original work had to be dropped, although I felt somewhat like a renegade in not pursuing the subject further, though I determined it was only a postponement. So last year I began the work again, and the paper before the Chicago Gynæcological Society last April was the result. In that I took the broad, firm ground that Remak's law has stood as a stone wall square across all true progress, and that it must give way if we ever expect to advance nearer to the sources of life than we have been for the last generation. It takes no cognizance of the formation of the mesoblast. We should study the individual in his present condition, it is true, with a recollection of what he has come from, but that in each varying state we must follow the simple common-sense law that Nature always changes the individual to suit his surroundings, and that we can not expect to find the conditions of the adult the same as those of the fœtus. It is simply an imposition on common sense to expect that the most destructible of all tissue—protoplasm—should depend upon itself for reproduction. To me what the three great membranes mean are the three great functions of the body. The epiblast undoubtedly makes the nervous system, and all that it contains; the hypoblast makes the digestive system, with all connected with it; and the mesoblast makes the locomotive and procreative apparatus, and all the weapons of defense; but that all three of these membranes undoubtedly make connective tissue and epithelium wherever necessary, or at least tissues which are very closely akin to both. Even in the fœtus I believe that our teachers have gone too far in laying down any such dogmatic rule as Remak's law. It did very well to work by for students, to nail down hard and fast the difference between connective tissue and epithelium, but now that we know positively that epithelium does spring directly from connective tissue, the whole structure has to fall to the ground. In that Chicago paper those of you who recollect it will remember that I gave drawings of many forms of epithelial tissue springing directly from connective tissue. There were secreting glands, feather papilla, dermal structures, etc., all of them showing the direct transition of protoplasm forming from connective-tissue threads into epithelium. In that paper I also took the ground that the sustentacular tissue directly underneath

the epithelium, not only of all secreting glands, but of all dermal structures, is closely allied to what has been called the reticular tissue, and that the reason it has not been recognized long ago is the fact that it is packed so densely for the purpose of forcing the protoplasm to grow to the outside that its fibrous nature is overlooked by low powers; but, under proper investigation, it undoubtedly is a structure very closely allied to the tissue that makes the framework of the lymphatic glands. So, then, one of the points that I wish to announce to-night firmly and unmistakably is that all those structures known as reticular tissue, the sustentacular tissue of all secreting glands, and the *stratum lucidum* of all dermal and mucoid structures, are closely allied, and that their function is, as I have stated in my opening sentence, to manufacture the protoplasm which supplies the waste incident to life.

It has been the custom of men when they made discoveries to invent new words to express their meaning. I dislike the habit, but, as some foreigners may not understand the meaning of the English language, it may be best to give it in the Greek. The Greek term would be anagenetic tissues, but, for fear some one may happen to find this paper who does not understand the English word thoroughly, I will give it all in Greek. It would be: Somanagenetic. You all understand what this means—*somna*, body; *ana* has the same force as the Latin " *re*," as in regenerate; and " *genomi*," which means to produce. Literally, in English, it means begetting the body again. Our English word regeneration covers the full force of the whole expression. So, then, to all of you I would like to introduce these varying and heretofore misunderstood structures as all belonging to the same class, which, named from its function, are the anagenetic tissues. Use this term or not, as you like, if you only remember what my beliefs about them are.

Some of my critics have said that I have not brought evidence enough to prove the ground I have taken about the budding of the granule from the thread, and what I here bring you is to me at least convincing. It consists, first, of three drawings on one card, containing cross sections of the growing feather of a turkey, showing first under the low power that the central core of the feather papilla is nothing but ordinary protoplasmic tissue, fed by blood vessels, and looking for all the world like one of the Malpighian bodies of the spleen. Directly around it you will see a zone of transition tissue from this protoplasm into epithelium. Then, still further out,

you see the darker columns which go to build up the shaft of the feather. The dark columns are the outside of the feather, as it lies against the bird's body, and the deposit of pigment, of course, gives the color of the bird. The light part, shown on the left-hand side of the 250 power, is the under side of the feather, which you all remember shows up white in most birds. This low-power sketch is a beautiful demonstration of the fact that the feather is nothing but a modified scale, for under this power it looks very much like a finger cut across through the nail, the nail representing the dark columns, with the pulpy part of the finger representing the inside of the feather, and the feather papilla itself representing the bone. By looking at this from a clinical standpoint, you can see what an ingrowing toe nail is. After all, it is nothing but a scale reverting to the type of the feather and getting too much in-curved.

The 800 power on this card represents the junction of the feather papilla and the inside of the feather. It speaks for itself, and shows the gradual transition from the protoplasm of the papilla to the young epithelial cells, which go to make the pithy soft inside of the feather.

The 3,000 power shows the opposite side of the same section, where the columns join on to the papilla. This section is rather thick, but still shows something of the fibrous nature of the papilla, and that the columns are first laid down in bundles of fibers, which are gradually converted into the columns.

Card No. 2 contains drawings of longitudinal sections of a six-weeks'-old chicken. In studying this remember that these are the first feathers grown after the chick comes out of the shell. It is hatched with a soft, downy covering of feathers, which are shed while these are being grown. The creature is growing very rapidly at six weeks, and the growth of its feathers must be proportionate.

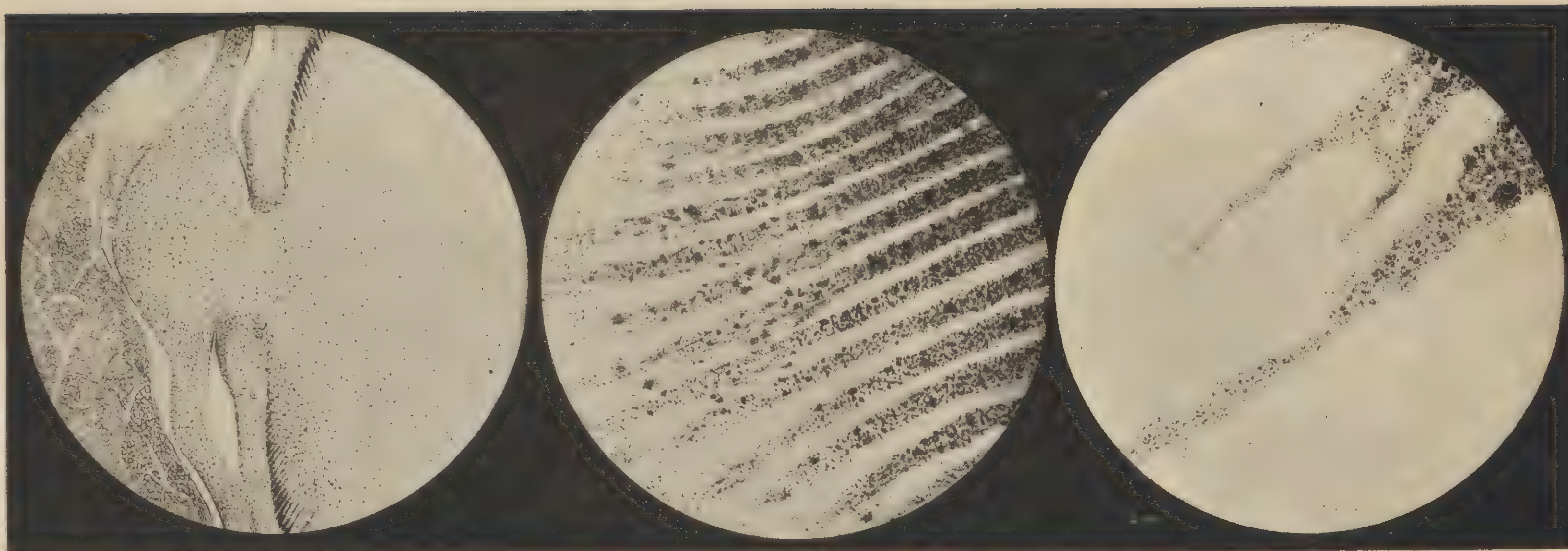
The 250 power is a beautiful demonstration of what I have said, that "the feather papilla is nothing but a local hypertrophy of the *stratum lucidum*." The root sheaths look like the bottom of a flask with a hole in the middle. Directly underneath this opening is a disklike enlargement of the *stratum lucidum.* From this thickening you see the new tissue pouring up through this opening to the inside of the cavity of the quill.

The second drawing is under the 800 power, and shows these bundles of fibers at the point where they are rapidly changing to

1 2 3

1. Cross-section of turkey-feather papilla, showing topography. 250 diameters.
2. Cross-section. Junction of feather papilla with inner side of growing feather. 800 diameters.
3. Cross-section. Junction of feather papilla and outer side of feather. 3000 diameters.

NOTE.—The following illustrations are reduced .267 in size from the author's drawings.—EDITOR.



4 5 6

4. Longitudinal section of feather. Six weeks' chicken. Showing local hypertrophy of the stratum lucidum as foundation of papilla. 250 diameters.
5. Upper part of papilla, showing transition of bundles of threads into epithelial columns. 800 diameters.
6. Same as No. 5. 3,000 diameters.

an epithelial nature. They speak for themselves, and need no description.

The 3,000 power shows one of these bundles at the same place, and gives you a better idea of how the transition takes place. These black dots are pigment. The feather happened to be an extremely black one, and its granules of protoplasm show pigment from the very start. The feathers of grown birds, as they change their plumage, form more perfect cells before the deposit of all this pigment. But in them the process of growth is slower than in the fledgling, and the consequence is that the papilla shows far many more round cells than you see here displayed. In fact, it is so much the case in some specimens that the fibrous nature of the papilla is more or less obscured by the number of round cells. So I have taken advantage of this fact to have a number of places showing the condition of the papilla in its middle and lower portions drawn on these separate cards. You see they are only bundles of minute fibers, with very few nuclei, but very rich in small granules, many of which show pigment.

The next chart, though, is to me the most convincing of all. It is a study of the young calf's liver. The 250 power shows the picture with which you are familiar, simply the lobules with the spokelike arrangement of the columns of hepatic cells radiating from the intralobular vein, with the spaces for the interlobular.

The 800 power shows that the interstices between the "spokes" contain a very fine network of not exactly homogeneous tissue, for a few granules appear under this power. But to a greater or less extent these fibers seem homogeneous, and the little specks, which represent the young corpuscles, might readily be overlooked if this were the only method for their investigation.

The 3,000 power, though, shows exactly the same thing for these fibers that I described as going on in the ultimate fibers of the endometrium. First, the little granule within the thread begins to swell. Slowly it enlarges until it protrudes from the side of the thread, and many times in its investigation you will see it has exactly the same staining reaction as the nucleus of the large cell beside it. By and by, however, you will see a little halo begin to show around some of these granules, like the penumbra shown in our old astronomies when we were studying the eclipse. This gets wider and wider, until little granules begin to show within this shadow. So then, as I have stated so often, as is the case in ade-

8 9 10

8. Calf's liver. 250 diameters.
9. Same as No. 8. 800 diameters.
10. Same as Nos. 8 and 9, showing gradations of development of granules into full grown liver cells. 3,000 diameters.

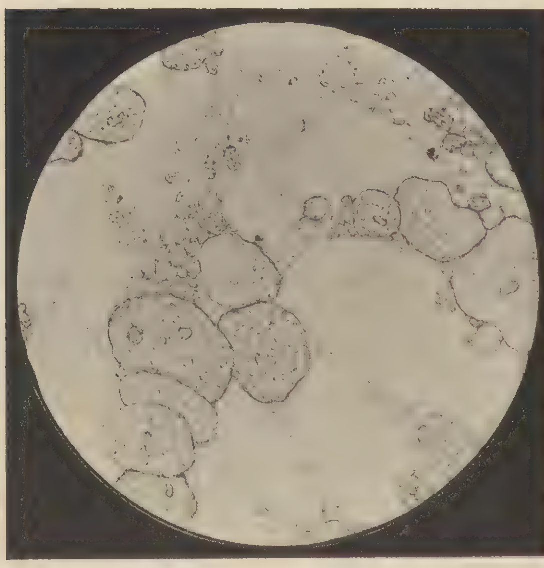
noid tissues everywhere, in the most typical of all epithelial structures, the liver, we find identically the same thing going on in the sustentacular tissue within the lobule.

One other proof this high power shows of the relation between what has heretofore been called connective tissue and epithelium is the direct connection, shown in these drawings, between the large protoplasmic cells and the threads themselves. The threads not only serve the purpose of holding the cell in place, but they have a direct organic connection with the protoplasm of the cell, through which it must certainly get its nervous control. One form of the argument on which Mr. Heape based his belief that the epithelium lining the endometrium of the monkey's uterus is produced directly from the subjacent endometrium was the continuance of the protoplasm of both structures with each other; and this is a very important point, and one, while I have used it mentally, I have not said much about.

Fearing that you might think these drawings schematic or more or less diagrammatic, I have had many other spots of the same specimen drawn, and they accompany this on the little single sheets. They are direct representations of what the microscope shows, not made by myself, but by my friend, Mr. Walter Berry, a medical student and a graduate of the Worcester Polytechnic School.

The reason that I have given you the different powers is to show you why this thing had been overlooked, and to accentuate some of the troubles I have had in finding it. The 300 is the power that you are all used to, for that is the one the histological laboratory first puts in the hands of its students, and many teachers tell them that there is no use ever using anything else—that what you can not find with that is not worth looking for. You see it only gives a sort of topographical view of the lobule, leaving the interstices perfectly light, and causing you to believe there is nothing between these rods of cells. The 800, though, demonstrates the fallacy, and shows you there are fibers there that in some places look suspiciously like granules, with some corpuscles that are undoubtedly very much smaller than others. But still there is not enough difference in their sizes, under this power, to base any positive conclusion upon. This is the highest power that is ordinarily used in laboratories, and very few men will take the trouble to work with anything greater. I say "trouble" advisedly, because the handling of a very high-power immersion lens is one of the

most difficult and exasperating pieces of work, all forms of surgery included. In the first place, your specimens must be the very thinnest that can possibly be imagined, and if you are attempting to cut tissues of different densities, like the feather and its pulp, nothing but the freezing microtome can possibly keep from tearing them apart. Next, they must be mounted in glycerin, and this, you know, is one of the most tedious of all forms of mounting, for, as I have already stated, Canada balsam blurs everything. Last, but by no means least, you simply have to wait until you get the right kind of light or you see nothing. From the first day of January to the seventh of April, this year, I have kept account of the days in which the immersion lens could be used. There have been only five days in which it could be used at all, and then only from eleven o'clock in the morning to two o'clock in the afternoon, and only two of these five days have been typical days. It is true this is the worst part of the whole year for this kind of work, for the sun is away in the south, and does not give us anything like the amount of light that it will in the summer months. It is also true that Cincinnati is about two hundred miles south of New York; it is also true that it is a very smoky city. The place in which this lens is used is to the northeast of the city, and our prevalent winds are from the southwest, so that the smoke is blown over our suburb a great many days in the year. And I remember distinctly that the two days in which this lens worked the best were when we were in the middle of a high barometric area, with the wind from the northeast. The cause of all this is the fact that the aperture of the lens is very little if any larger than the head of a cambric needle, and the pencil of light which it admits is the very smallest, and magnified to the size that you see in these drawings, you can imagine how attenuated this pencil would be. So, then, to any man who attempts to follow my tracks, I must say there is nothing for him to do but to possess his soul in patience even after he has a specimen made, and wait until he gets the right light before he can say either yea or nay as to whether what I tell you is true or false. I would think that the climate of Arizona would be typical for the use of this lens. I have said, in other papers, that my belief for the reason that the Berlin school dislikes the high powers and the Viennese school is partial to it is the difference in latitude. I have tried all forms of artificial lights, and none of them have proved equal to the natural light of a bright clear day. There



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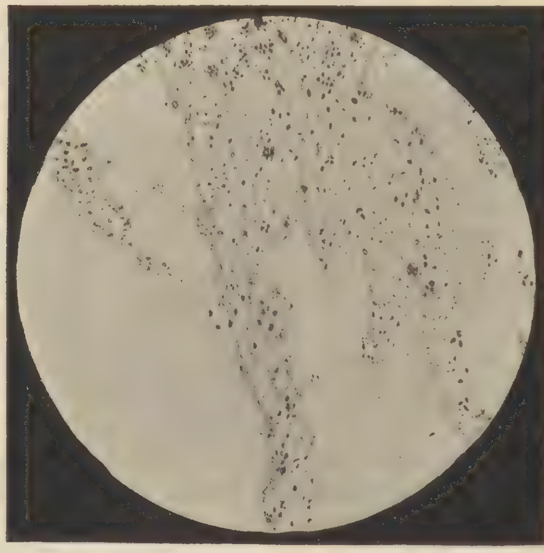

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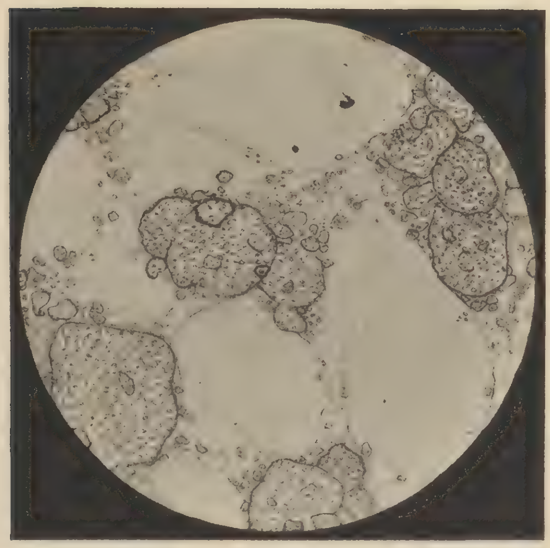
11. Same as Nos. 8 and 9, showing gradations of development of granules into full grown liver cells. 3,000 diameters.
7. Middle of papilla. 3,000 diameters.



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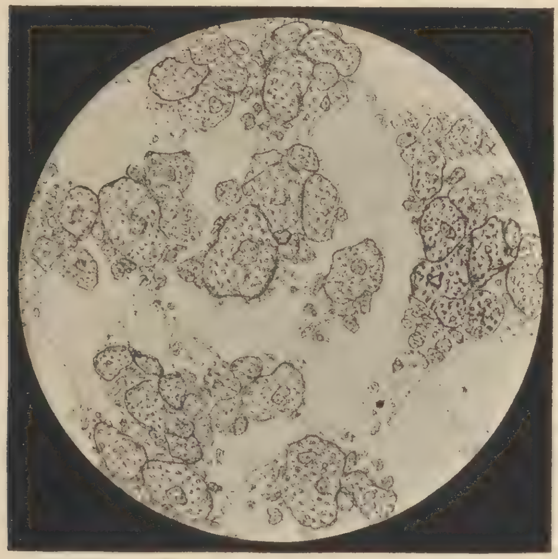

13

12 and 13. Same as Nos. 8 and 9, showing gradations of development of granules into full grown liver cells. 3,000 diameters.

is something about the absorption bands of the sodium which blurs everything, and makes you uncertain what you are about. The reflected electric lights give such deep shades that you have the same uncertainty as to the shadow and substance under the microscope that you have on the streets when looking at distant objects under the electric light. Whether these difficulties will ever be obviated I can not say. My work has had to be done in half hours scraped together, snatched from a busy practice, and I have had no time recently to experiment with the various forms of our new lights, but I sincerely hope that some one will some day overcome these difficulties, and place the lens within reach of all of us; but, until that day comes, nothing but patience will overcome these difficulties. So much for methods.

Now for the character of these anagenetic tissues themselves. My belief is, with the exception of the nervous system, they are the most highly vitalized of all the structures within the body. They are very closely connected with the nerves themselves. In the first place, they follow the routes of the blood currents, and in many places, as in the spleen, they are direct offshoots of the vessels themselves. The specimens before you show that these threads must be direct outgrowths from the capillaries within the lobule. The rich supply of the vasomotor nerves to all this vascular tissue you know as well as I do. You also know how intimate is the association of the *stratum lucidum* with the capillaries of the intestine. The same thing holds good in the papillæ of the skin, in the sebaceous follicles, in the hair follicles, and, as demonstrated before you here, in the feather papilla itself. And if we have one fundamental law laid down by which we work it is that the vasomotor nerves are omnipresent. The shape of the tissue reminds you very much of a stellate ganglion cell, and it would not surprise me after all if some day it is proved that this reticular tissue is nothing more or less than a third division of the nervous system itself, which has so far been overlooked. The branching of the stellate cells is very similar in form to the branchings of the reticular tissue. Its connections with the sympathetic we are taught with our first lessons in histology. So my belief is that these granules are controlled directly by the sympathetic system, if, in fact, their matrix is not a part of it. But, no matter how that may be, I am sure, as I stated in my opening sentence, that the protoplasm we will use up next week or next month is to-day being manufactured

by our nervous systems, and that the repair of the body is accomplished directly by one central control, and is not left to the haphazard pleasure of millions of little perishable entities. After all, Virchow understood this better than all the investigators who have followed him. I know that the life of a cell is typified by that of a leaf; that it is budded out from the parent stem; that it grows to its full maturity; that it is used by the economy for a greater or less length of time, and that sooner or later it drops into an age of obscurity and is thrown off as foreign matter; and that this law holds good particularly for the epithelial cells, and ultimately for every cell within the body.

Before we turn to the pathological side of this subject, there is one other point I wish to speak of, and that is in every tissue and living fluid of the body every histologist speaks of granular matter. At last we know where these granules come from. They are swept out of the lymphatic glands, the spleen, and the adenoid structures everywhere and carried into the blood, and these very little granules, half grown, are the ones the physiologists have been telling us so much about under the name of hæmatoblasts. For I believe that the granule, once set free from the thread, is nothing but a minute mass of vital energy which has the power not only to go on to the formation of a cell, but to the subdivision of that cell, and to work out for itself *and its line* all that we have been taught heretofore about the subdivisions and performances of cell life, particularly those of the blood and epithelial cells.

If this view be true, as I am sure it is, many of our pathological ideas must be reconstructed, and it is that I wish specially now to bring to your attention. First and foremost, the old idea of new growths being dependent upon fœtal cells that have lain dormant for forty, fifty, or sixty years, must be swept away. The improbability of this doctrine was shown me years ago in reading the experiments of some German with periosteum in the lungs of chickens. Many of you will remember that these little bits placed in the jugular vein were examined after months of residence in the lung. In a few weeks they were firmly anchored; in a few more, bone was beginning to be formed; shortly afterward, almost perfect Haversian systems were found in these pulmonary infarcts. But, strange to say, at the end of six months every one of them had entirely disappeared, showing that there must be a central nerve control which resents the intrusion of any foreign substance, no matter

how highly vitalized, and that if it lives at all it must be because it is sufficiently strong to resist the " trophic control " which every man believes the body possesses.

The next subject which I will ask you to study in this light is that of fibrosis in all its forms. It explains at once those heretofore inexplicable cases of cirrhosis of many organs. If the protoplasm is being made in these threads all the time, and the organ becomes slightly irritated, the protoplasm makes connective tissue instead of the higher specialized epithelium, and the destruction of the organ is a foregone conclusion. Last, but not least, the subject on which it has the strongest bearing, as I have already intimated, is that of new growths. At last it gives us a clew as to what they really are. I have just shown you how intimately these structures are connected to the nervous system, and how rich must be the supply of nerve connections with it. Suppose for some reason, by a trauma or in some other way, the tracks through which this nerve control is exercised should be interfered with, the tissues are left like a foreign colony cut off from the mother nation. The result of this you easily understand. The first thing, of course, if the connection is not absolutely cut, we would expect would be homologous growths; if, however, this separation is absolute, the tissues are ready for any kind of rebellion, and, left to themselves, the " histological mob " may be the result. As one of my *confreres* says, " A theory worked out in the laboratory that will not stand a clinical test is not worth the paper it is written on." But I claim for this that it not only stands all clinical tests, but it makes very simple many of our pathological riddles. Take carcinoma, for instance. Ever since the early dawn of surgery, trauma has been supposed to play a large *role* in its ætiology, and within the last few years many of our most thoughtful men have begun to think that a condition approaching neurasthenia also plays a greater or less part. Given these two conditions, and the fact the protoplasm is made steadily every day that it has been cut off from its nerve supply, you see at once how carcinoma might originate. You also understand how it is that some carcinomæ may begin in an adenomæ, there being a gradual change to the malignant type. You also understand why it is that a cancer may suddenly begin and grow very rapidly, after having lain quiet for a long, long time.

To take an illustration of a case: An irritated lip from an old tobacco pipe, with slight eczematous eruptions, which may have

ultimated in a small papillomata. This has lain more or less quiet for years. You know that around its base there is more or less infiltration of leucocytes going on during the whole of this irritation. You know that this budding off of the granules has made more and more cells, and, between the protoplasm manufactured on the spot and the migratory corpuscles which have come in to do police duty around the irritated place, sooner or later a band of lymph has to a certain extent isolated the papilloma from the rest of the body. The irritation kept up, this exudate is bound to be formed into connective tissue. The secondary contraction of this connective tissue is nothing but a form of fibrosis. If this contraction go on far enough, the nerve supply may be seriously interfered with. But the tips of the papillæ which are on the distal side of this fibrous band still have the power of reproducing protoplasm. The nerve supply once cut, this may go on indefinitely. The cell division, which I have said I believe Nature reserves for just such occasions, when phagocytic action is needed most, and the construction of new tissue is most required, comes in to do its rapid work. But if the trophic nerves have been severed by this band, the tissues are left to their own sweet will, and the kind of tissue they will produce no one can say. First, it may be nothing but a benign papilloma. But, left to go on, and not getting their wonted nerve control, sooner or later the nerve power with which they started out becomes weakened, and the new cells they have produced by this subdivision are of a far weaker character, and the result sooner or later will be a tissue which simply can not live. As long as the health of the individual behind it is perfect, any wandering cells that may get into the blood vessels and be swept away to other parts of the body are destroyed and handled by the good strong cells that they there come in contact with. But let some overpowering shock come to the nervous system of this individual, and the cells throughout his body become lowered in vitality, and he will no longer be able to resist this invasion, and the spreading of cancer is the result. How often is it in our experience that the death of a child, of a husband, the loss of money, the unfaithfulness of a partner in life, or some other such terrific shock only shortly precedes the rapid growth and general dissemination of a neoplasm that had before that been thought to be scarcely worth noticing. One other argument I have to bring to the proof of this is that no man ever saw a nerve in a carcinoma or sarcoma,

though a few have been described in benign growths. Of course, the sarcomas of early childhood have not this neurasthenic element in them, and the only way we can explain them is that the nerve control has either not been made correctly or that by some accident they have been cut off from the very start. If this is true, we understand at once why new growths are so apt to spring up in useless organs that have passed their functional activity, and which the economy is trying to get rid of.

This, Mr. President, is only one of the many riddles which will become plain if this doctrine is correct. The enumeration of them, though, would be tedious, and all I have hoped to do to-night is to state plainly that our protoplasm is made by specific organs, which are laid down from the formation of the being, and that it is their function to make the protoplasm just as much as it is the function of the stomach to make the gastric juice. The most important function of the body—that of the production of protoplasm—was never intended to be left to the haphazard way we have heretofore been taught. I fear I have been tedious in many places, but my only apology for it is to show you the difficulties that I have met, and to blaze out the road, as it were, for those who are to follow me. Until a man has gone through with these experiments carefully and faithfully, his word is worth nothing. The manufacture of protoplasm only by cell division is simply an hypothesis, but the growth of these granules is a reality—one that any one can see if he will only take the time and patience to prepare his specimens properly, and wait until he gets the proper kind of light. Even an ordinary hazy day will not do; nothing but the greatest number of rays condensed into the smallest space without shadow can possibly do the work. As I have not been able to find any one who has worked it in this way, I do not expect to answer the criticisms that I know this will bring down on my head from any one who has not followed out the route that I have here laid down. I give you these facts in the hope that some one will be stimulated to follow along the same line and push it even further than I have done, for the fields that it opens up, not only in physiology but in pathology, are away beyond our vision.

In closing, let me thank you for the somewhat incredulous attention which you have given me, for a thing that has taken me twenty years to work out I do not expect to be grasped in a few minutes. I do not ask you to accept these doctrines until you have

tested them for yourselves; but it seemed to me that the most fitting mouthpiece I could select would be the leading body within the shadow of my old Alma Mater. All I can ask is that you weigh the evidence carefully, that some of you do the work over again, for, even though this may not be the exact route, yet somewhere near it I am sure lies the road to our future progress.